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David W. Highet, VP & Chief IP Counsel
Becton, Dickinson and Company
(Antonelli, Terry, Stout & Krause, LLP)
1 Becton Drive, MC 110
Franklin Lakes, NJ 07417-1880

EXAMINER	
DEJONG, ERIC S	

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte ROBERT L. CAMPBELL, PERRY D. HAALAND,
DOUGLAS B. SHERMAN, WALTER WILLIAM STEWART II,
and SHEILA A. LLOYD

Appeal 2009-008143
Application 09/359,260
Technology Center 1600

Decided: January 4, 2010

Before DONALD E. ADAMS, ERIC GRIMES, and
JEFFREY N. FREDMAN, *Administrative Patent Judges*.

FREDMAN, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 involving claims to a method of identifying a peptide with a desired activity. We have jurisdiction under 35 U.S.C. § 6(b). We reverse.

Statement of the Case

The Claims

Claims 76, 82-90, 92-95, 131, 132, and 134-138 are on appeal. Claims 135 and 137 are representative and read as follows:

> 135. A method of identifying a peptide with a desired activity having an indicia that satisfies a test requirement, the method comprising the steps of:
>
> identifying a predetermined set of peptides;
>
> parameterizing the predetermined set of peptides by:
>
> determining a first parameter for each predetermined peptide, wherein the first parameter is a whole molecule parameter, and
>
> determining a second parameter for each predetermined peptide, wherein the second parameter is dependent on the specific order of constitutive subunits within each predetermined peptide;
>
> performing a space-filling design of the parameterized peptides to identify first test peptides;
>
> constructing a first test peptide library comprising a plurality of first test peptides identified using the space-filling design, wherein the length of said first test peptides comprises about four amino acids to about twenty amino acids, and wherein said first test peptides are a subset of said predetermined set of peptides;
>
> determining an activity, having an indicia, of said plurality of first test peptides;

measuring the indicia of said activity for said plurality of first test peptides;

deriving a quantitative relationship between said indicia of said activity, said first parameter, and said second parameter;

calculating an estimated indicia for each remaining peptide from said predetermined set of peptides using said quantitative relationship;

setting a test requirement, based on a desired activity, having a test indicia range;

selecting a second test peptide library comprising at least one second test peptide, wherein each second test peptide has an estimated indicia that satisfies said test requirement, and wherein said second test peptides are not in said first test peptide library;

measuring the indicia of each second test peptide; and

identifying at least one second test peptide having a measured indicia that satisfies said test requirement.

137. A method of identifying a peptide with a desired activity having an indicia that satisfies a test requirement, the method comprising the steps of:

identifying a plurality of initial peptides having a length of about four amino acids to about twenty amino acids;

parameterizing the initial peptides by:

determining a first parameter for each initial peptide, wherein the first parameter is a whole molecule parameter, and

determining a second parameter for each initial peptide, wherein the second parameter is dependent on the specific order of constitutive subunits within each initial peptide;

performing a space-filling design of the parameterized peptides to identify first test peptides;

constructing a first test peptide library comprising a plurality of test peptides identified using the space-filling design, wherein said first test peptides are a subset of said initial peptides;

measuring the indicia of an activity of said plurality of test peptides;

deriving a quantitative relationship between said indicia of said activity, said first parameter, and said second parameter of said plurality of test peptides;

calculating an estimated indicia for each initial peptide using said quantitative relationship;

setting a test requirement, based on a desired activity, said test requirement having a test indicia range;

selecting a second test peptide library comprising at least one second test peptide, wherein each second test peptide has an estimated indicia that satisfies said test requirement, and wherein said second test peptides are not in said first test peptide library;

measuring the indicia of each second test peptide; and

identifying at least one second test peptide having a measured indicia that satisfies said test requirement.

The prior art

Cramer et al. US 6,240,374 B1 May 29, 2001

Ostrem et al., *Discovery of a Novel, Potent, and Specific Family of Factor Xa Inhibitors via Combinatorial Chemistry*, 37 BIOCHEMISTRY 1053-1059 (1998).

The issues

A. The Examiner rejected claims 76, 82, 87-90, 92-95, 131, 132, 134, and 135 under 35 U.S.C. § 102(b) as anticipated by Ostrem (Ans. 3-9).

B. The Examiner rejected claims 76, 82-90, 92-95, 131, 132, and 134-138 under U.S.C. § 103(a) as obvious over Ostrem and Cramer (Ans. 9-10).

A. 35 U.S.C. § 102(b) over Ostrem

The Examiner finds that "Ostrem et al. sets forth a procedure for drug discovery by the preparation of a octamer combinatorial test peptide library in order to identify leads compounds therein, which reads on the claimed limitation of identifying a predetermined set of peptides" (Ans. 4).

Appellants argue that "there is no showing of where, or how, Ostrem discloses each step recited in the claimed invention" (App. Br. 21). Appellants argue that "Ostrem itself discloses that a complete representation of peptides in the library was not known, as only a select few peptides were confirmed as being available after activity assays were completed" (App. Br. 21). Appellants argue that "Ostrem's selection of the split-synthesis method clearly supports the fact that a space-filling design was not applied" (App. Br. 22).

In view of these conflicting positions, we frame the anticipation issues before us as follows:

(i) Have Appellants demonstrated that the Examiner erred in finding that Ostrem teaches "calculating an estimated indicia for each remaining peptide using said quantitative relationship"?

(ii) Have Appellants demonstrated that the Examiner erred in finding that Ostrem teaches "performing a space-filling design of the parameterized peptides"?

Findings of Fact (FF)

1. The Specification teaches that "[c]ompound libraries can be made by any method known in the art" (Spec. 16, l. 20).

2. The Specification teaches that "[i]t is not necessary that all of the test compounds in the first test library actually be synthesized and/or isolated, *e.g.*, the library may be a 'virtual' library" (Spec. 25, ll. 5-7).

3. The Specification teaches that the:

> term 'space-filling design' as used herein is intended to be construed broadly and includes all such techniques known to those skilled in the art. Exemplary space-filling designs include but are not limited to full factorial designs, fractional factorial designs, maximum diversity libraries, genetic algorithms, coverage designs, spread designs, cluster based designs, Latin Hypercube Sampling, and other optimal designs (*e.g.*, D-Optimal), and the like.

(Spec. 19, ll. 17-23).

4. The Specification teaches that "[a]ny parameter (i.e., descriptor) known in the art that can be applied to characterize a compound may be used to carry out the present invention. Physical, chemical (including biochemical), biological and/or topological parameters may be employed to determine the relationship" (Spec. 27, ll. 22-25).

5. The Specification teaches that a "'whole molecule parameter' is a value that characterizes a molecule irrespective of the arrangement of its constitutive atoms. For example, a whole molecule parameter for a peptide is one that does not depend on the order or sequence of the amino acids in the peptide" (Spec. 28, ll. 2-6).

6. The Specification teaches that "[i]llustrative parameters that may be employed . . . include but are not limited to molecular weight, charge, isoelectric point, total dipole moment, isotropic surface area, electronic charge index, and hydrophobicity" (Spec. 28, ll. 15-18).

7. The Specification teaches that the "relationship determined between the parameter(s) of the first test compounds and the indicia of the measured property can be determined by any method for describing the interaction between the activity and structure of compounds" (Spec. 8, ll. 15-18). The Specification teaches examples of this determination, such as "quantitative structure-activity relationships (QSAR), nearest neighbor analysis, self organizing maps, or other machine learning and statistical techniques" (Spec. 8, ll. 18-20).

8. The Specification teaches two mathematical formulas for calculating relationships between parameters (Spec. 8, l. 21 to 9, l. 17).

9. The Specification teaches "a method of predicting the activity of a peptide . . . A relationship (e.g., a mathematical relationship) is determined between a measured indicia of an activity (e.g., a biological activity) of a plurality of peptides from a test peptide library and at least one parameter" (Spec. 12, ll. 6-10).

10. Ostrem teaches "[s]creening an octamer L-amino acid library with biotinylated human factor Xa conjugated with streptavidin alkaline phosphatase" (Ostrem 1053, col. 2).

11. Ostrem teaches that the "biotinylated factor Xa-SAP mixture was added to library beads . . . and incubated for 1 h with gentle mixing" (Ostrem 1054, col. 1).

12. Ostrem teaches that the beads were washed and then "incubated with substrate solution . . . until color developed on individual beads . . . Beads with uniform blue color were picked from the library" (Ostrem 1054, col. 1).

13. Ostrem teaches that "[b]eads picked from the library which show no staining when incubated with active-site inhibited factor Xa . . . were briefly stripped and destained, then incubated with uninhibited factor Xa and SAP. Beads which restained were submitted for sequencing by Edman degradation" (Ostrem 1054, col. 1).

14. Ostrem teaches that the peptides were tested in a Factor Xa assay, in protease specificity assays, in a prothrombinase assay, and in coagulation assays (Ostrem 1054, col. 2 to 1055, col. 1).

15. Ostrem teaches that "[t]o determine whether the tripeptide binds in a substrate-like mode which might be converted into a more potent mechanism-based inhibitor, C-terminal p-nitroanilide (pNA) substrates of Tyr-Ile-Arg were synthesized and compared for hydrolysis by factor Xa, thrombin, and trypsin" (Ostrem 1056, col. 1).

16. The Examiner finds that the "large number of varying peptide sequences in a peptide library are certainly 'space-filling' elements, and the

applied combinatorial approach using a significant sampling of alternative peptide sequences is considered a 'design'" (Ans. 5).

17. The Examiner finds that:

> inhibition of factor Xa activity is shown in Figure 1 (see Ostrem et al., page 1055), which includes values of inhibition activity measured at several peptide concentrations and the calculation of sigmoidal curves that are fit to the measured factor Xa inhibition values. The calculation of these sigmoidal curves is based on the measured Xa inhibition values and are used to extrapolate the inhibition of peptides over concentrations ranges which were not directly measured and, therefore, teaches the derivation of a quantitative relationship between the measured indicia (factor Xa inhibition), the first parameter (octamers having a potency of 4 to 15 □M [sic, μM] and retaining an unusual selectively for factor Xa over thrombin), and the second parameter (octamers comprising a specific tri-peptide sequence).

(Ans. 6.)

Principles of Law

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros., Inc. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). Analysis of whether a claim is patentable over the prior art under 35 U.S.C. § 102 begins with a determination of the scope of the claim.

We determine the scope of the claims in patent applications not solely on the basis of the claim language, but upon giving claims their broadest reasonable construction in light of the specification as it would be

interpreted by one of ordinary skill in the art. *In re Am. Acad. Of Sci. Tech. Ctr.*, 367 F.3d 1359, 1364 (Fed. Cir. 2004).

Analysis

Each of the independent claims on appeal requires a step of "deriving a quantitative relationship between said indicia . . . , said first parameter, and said second parameter" and then "calculating an estimated indicia for each remaining peptide . . . using said quantitative relationship" (Claims 135, 136, 138) or "calculating an estimated indicia for each initial peptide using said quantitative relationship" (Claim 137). This calculation is performed by testing a portion of a peptide library, the "predetermined set of peptides", to determine indicia of an activity. That information is used to derive a quantitative relationship between the indicia and the first and second parameters of the peptides; the quantitative relationship is then used to calculate "estimated indicia" for the remaining portion of the peptide library (*see* Claim 135).

The Examiner finds that Ostrem teaches "calculation of sigmoidal curves that are fit to the measured factor Xa inhibition values" (Ans. 6; FF 17). The Examiner reasons that the "calculation of these sigmoidal curves is based on the measured Xa inhibition values and are used to extrapolate the inhibition of peptides over concentrations ranges which were not directly measured and, therefore, teaches the derivation of a quantitative relationship between the measured indicia" (Ans. 6; FF 17).

We do not agree with the Examiner's interpretation of Ostrem as it relates to the instant claims. The lines in Figure 1 of Ostrem represent relative rates of Factor Xa inhibition plotted against concentrations of three

particular peptides (and the inhibitor tenstop). Any extrapolation represented by the lines drawn between tested points is an extrapolation of predicted rates of Xa inhibition by the three tested peptides at other concentrations. These lines provide no information regarding the inhibition activity or any other indicia of the remaining portions of Ostrem's peptide library.

Ostrem therefore does not describe a step of "calculating an estimated indicia for each remaining peptide using said quantitative relationship" as required by the claimed invention.

Additionally, each of the independent claims requires "performing a space-filling design of the parameterized peptides" (Claims 135-138). We recognize that the Specification states that the "term 'space-filling design' as used herein is intended to be construed broadly and includes all such techniques known to those skilled in the art" (Spec. 19, ll. 17-19; FF 3). However, all of the specific examples disclosed in the Specification for space-filling designs represent computer modeling methods (FF 3).

The Examiner reasons that "the "large number of varying peptide sequences in a peptide library are certainly 'space-filling' elements, and the applied combinatorial approach using a significant sampling of alternative peptide sequences is considered a 'design'" (Ans. 5; FF 16).

We do not agree with the Examiner's interpretation of "performing a space-filling design" in light of the instant Specification as it would be interpreted by one of ordinary skill in the art. While the Specification states that the term should be "construed broadly", this breadth is limited to techniques "known to those skilled in the art" (Spec. 19, ll. 17-19; FF 3).

Space-filling design is a term of art in bioinformatics which the skilled artisan would have known does not refer to peptides themselves, but is drawn to making virtual representations of these peptides. We do not interpret these claims to encompass actual peptides as "space-filling", but rather to solely encompass virtual representations of peptides for this claim element, based upon computer modeling methods such as those disclosed in the Specification (FF 3). Ostrem therefore does not describe a step of "performing a space-filling design" as reasonably understood by the skilled artisan.

Conclusions of Law

(i) Appellants have demonstrated that the Examiner erred in finding that Ostrem teaches "calculating an estimated indicia for each remaining peptide using said quantitative relationship".

(ii) Appellants have demonstrated that the Examiner erred in finding that Ostrem teaches "performing a space-filling design of the parameterized peptides".

B. 35 U.S.C. § 103(a) over Ostrem and Cramer

The Examiner finds that "Ostrem et al. sets forth a procedure for drug discovery by the preparation of an octamer combinatorial test peptide library in order to identify lead compounds therein" (Ans. 9). The Examiner finds that "Ostrem et al. does not teach the parameterization of a predetermined set of peptides using a first and second parameter selected from the groups recited in instant claims 83-86" (Ans. 9). The Examiner finds that "Cramer et al. sets forth a method of validating molecular structural descriptors that may be used to select optimally diverse subsets of molecules with a desired

set of characteristics" (Ans. 10). The Examiner concludes that it would have been obvious to:

> parameterize peptides on the basis of molecular weight and hydrophobicity, as taught by Cramer, in the procedure for drug discovery as set forth by Ostrem et al. where the motivation to do so is found in Cramer et al., who teaches that the optimizing the characteristics of compound libraries utilized in drug discover[y] is critical for establishing a sufficiently diverse but manageable set of starting compounds for further investigation.

(Ans. 10.)

Appellants argue that "[a]s previously discussed, Ostrem clearly fails to disclose numerous features recited in independent claim 135. The inclusion of Cramer as a secondary reference does nothing to remedy this shortcoming, since Cramer also fails to disclose or suggest the same features" (App. Br. 38). Appellants argue that "Ostrem and Cramer do not even appear to be properly combinable for arriving at the claimed invention, because neither reference provides any motivation to seek out the teachings of the other with a realistic expectation of arriving at the claimed invention" (App. Br. 38-39).

In view of these conflicting positions, we frame the obviousness issue before us as follows:

Have Appellants demonstrated that the Examiner erred in concluding that Claims 135-138 would have been obvious over the combination of the structural descriptors of Cramer with the combinatorial chemistry method of Ostrem?

Findings of Fact

18. Cramer teaches analysis using "a set of related properties such as . . . molecular weight, estimate of hydrophobicity" (Cramer, col. 62, ll. 41-42).

Principles of Law

The Examiner has the initial burden of establishing a prima facie case of obviousness under 35 U.S.C. § 103. *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992) ("[T]he examiner bears the initial burden, on review of the prior art or on any other ground, of presenting a *prima facie* case of unpatentability.").

"[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006) (quoted with approval in *KSR Int'l v. Teleflex Inc*., 550 U.S. 398, 418 (2007)).

Analysis

Ostrem does not teach either of the steps of "calculating an estimated indicia for each remaining peptide using said quantitative relationship" or "performing a space-filling design of the parameterized peptides" as discussed above. The Examiner has not shown where Cramer teaches the steps which are absent from Ostrem. Thus, even combining Cramer's use of structural descriptors with Ostrem's combinatorial chemistry method, the combination does not suggest all the steps required by Claims 135-138.

Conclusion of Law

Appellants have demonstrated that the Examiner erred in concluding that Claims 135-138 would have been obvious over the combination of the structural descriptors of Cramer with the combinatorial chemistry method of Ostrem.

SUMMARY

In summary, we reverse the rejection of claims 76, 82, 87-90, 92-95, 131, 132, 134, and 135 under 35 U.S.C. § 102(b) as anticipated by Ostrem.

We reverse the rejection of claims 76, 82-90, 92-95, 131, 132, and 134-138 under U.S.C. § 103(a) as obvious over Ostrem and Cramer.

REVERSED

dm

DAVID W. HIGHET, VP & CHIEF IP COUNSEL
BECTON, DICKINSON AND COMPANY
1 BECTON DRIVE, MC 110
FRANKLIN LAKES NJ 07417-1880